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| 09/673,707 | 01/11/2001 | Ira H. Pastan | 15280-3561US | 3958 |

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| EXAMINER |
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ZEMAN, ROBERT A

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| ART UNIT | PAPER NUMBER |
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1645

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|--------------------------------------|--------------------------------------|--|
| Office Action Summary | Application No. 09/673,707 | Applicant(s) PASTAN ET AL. | |
| | Examiner Robert A. Zeman | Art Unit 1645 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) 19-24, 59-65, 79-88, 90-97, 99 and 101-103 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 9, 11, 52, 55, 57, 68-75 and 77 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 1-7,9,11,19-24,52-55,57,59-65,68-75,77,79-88,90-97,99 and 101-103.

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DETAILED ACTION

The amendment filed on 1-24-2007 is acknowledged. Claims 1-5, 19-24, 52-55, 59-62, 68-71, 74, 79-82 and 90-93 have been amended. Claims 1-7, 9, 11, 19-24, 52-55, 57, 59-65, 68-75, 77, 79-88, 90-97, 99 and 101-103 are pending. Claims 19-24, 59-65, 79-88, 90-97, 99 and 101-103 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claims 1-7, 9, 11, 52, 55, 57, 68-75 and 77 are currently under examination.

Declaration

The Declaration by Dr. David J. Fitzgerald filed on 10-16-2006 is acknowledged and has been fully considered.

Priority

In light of the amendment to the instant claims, Applicant's claim for priority is deemed perfected as SEQ ID NO:2 is disclosed in all priority documents.

Claim Rejections Withdrawn

The rejection of claims 1, 52, 55, 68 and 74 under 35 U.S.C. 112, second paragraph, as being rendered indefinite by the recitation of "SEQ ID NO:1" within parentheses is withdrawn in light of the amendment thereto.

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Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-6, 9, 11, 52-55, 57, 68-72, 74-75 and 77 under 35 U.S.C. 103(a) as obvious over Matsushita et al. (Aids Research and Human Retroviruses Vol. 6 No. 2, 1990, pages 193-203) in view of Barbas et al. (PNAS Vol. 91, 1994, pages 3809-3813 – IDS-5) and Pastan et al. (U.S. Patent 5,458,878 – IDS-5) is maintained for reasons set forth in the previous Office action in the rejection of claims 1-6, 8-9, 11, 52-55, 57, 68-72 and 74-77. The cancellation of claims 8 and 76 has rendered the rejection of those claims moot.

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Applicant argues:

1. The CD4-PE toxins will only bind to cells expressing gp120 as CD4 does not bind to itself.
2. The hepatotoxicity associated with CD4-PE cannot be attributed to the CD4-PE toxins as hepatocytes do not express CD4.
3. The basis of maintaining the rejection was that the CD4-PE toxins bind to a different target than the present invention and therefore are not analogous.
4. The 0.5 β antibody of Matsushita only binds to a single type of HIV-1 whereas the immunotoxin of the instant invention (and the CD4-PE immunotoxin) is not type-specific. Hence, any motivation Matsushita provided to create was removed by the failure of the CD4 toxins that are more broadly applicable.
5. Dr. Fitzgerald states that there is no reason to think that the hepatotoxicity observed in the trials of the CD4-PE toxin would not be found with respect to the toxins targeted by the antibody of Matsushita.
6. Dr. Fitzgerald argues that even if Matsushita provided motivation to make Env-targeted toxins prior to the CD4-PE trial, the failure of the CD4-PE immunotoxin in clinical trials removed said motivation.
7. Matsushita does not meet the long felt need for AIDS treatments.
8. The data presented by Goldstein was not available to persons of skill in the art at the time of the invention and hence cannot be used to support the conclusions regarding the Matsushita reference.

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Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, the Examiner acknowledges Applicant's argument that CD4-PE toxins will bind to cells expressing gp120.

With regard to Point 2, the Examiner did not state that the hepatotoxicity was due to the direct binding of the CD4-PE toxin to hepatocytes but that said toxin "disrupted some cellular or endocrine cascade present in man but not in the mouse"

With regard to Point 3, the rejection was maintained based on the fact that Matsushita's immunotoxin was shown to have efficacy. Since Matsushita's immunotoxin comprises the same components (i.e. a PE toxin and an anti-gp120 antibody) its demonstrated efficacy would have a greater impact on the skilled artisan than the failure of a immunotoxin comprising differing components (i.e. a PE toxin and CD4).

With regard to Point 4, contrary to Dr. Fitzgerald's assertion, it is deemed that the type specificity of the 0.5 β antibody would provide motivation for the skilled artisan to substitute it with a more broadly applicable antibody such as 3B3.

With regard to Point 5, given that the components of the two immunotoxins are different one cannot predict whether they would have the same effects *in vivo*. Moreover, as Applicant has provided no proof substantiating their speculative assertion, it is deemed non-persuasive. Finally, the basis of the rejection is whether the skilled artisan based on the efficacy demonstrated by the Matsushita immunotoxin would have been motivated to modify it, not whether the resulting immunotoxin would be successful in clinical trials.

With regard to Point 6, since Matsushita's immunotoxin comprises the same components (i.e. a PE toxin and an anti-gp120 antibody) its demonstrated efficacy would have a

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greater impact on the skilled artisan than the failure of an immunotoxin comprising differing components (i.e. a PE toxin and CD4). Following Dr. Fitzgerald's logic a failure of any given treatment modality would forever dissuade any study of not only that treatment modality but any modality that is similar to it. This is not the methodology used by the artisans in the biomedical arts.

With regard to Point 7, there existed then as there exists today a need for AIDS treatments. This need would motivate the skilled artisan take the immunotoxin of Matsushita and modify it to overcome its shortcomings. The fact that the 0.5 β antibody has never been brought to preclinical development is off-point. Given that despite its shortcomings (i.e. type specificity etc) the immunotoxin of Matsushita was demonstrated to have efficacy the skilled artisan would have been motivated to "fine tune" said immunotoxin by utilizing an antibody with broader applicability in order to try and develop a highly desired treatment modality. Again, whether the resulting immunotoxin would be successful in clinical trials is irrelevant, the issue is whether or not the skilled artisan would have been motivated to modify the immunotoxin of Matsushita. For the reasons set forth above, the skilled artisan would have been motivated to make such a modification.

With regard to Point 8, the Goldstein reference was not referred to lend support for the motivation to modify Matsushita but as a supporting the validity of the Matsushita reference.

As outlined previously, Matsushita et al. disclose anti-pg120 immunotoxins comprising the 0.5 β antibody coupled to the *Pseudomonas* exotoxin (see abstract). Matsushita et al. differs from the instant invention in that they don't disclose the use of the 3B3 antibody or the use of altered PE40. Barbas et al. disclose a human antibody to gp120 (3B3) with broad strain cross-

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reactivity (see page 3812-3813). Pastan et al. disclose modifications of the carboxyl terminus of the PE molecule resulting in increased cytotoxicity (see abstract and column 3, line 27 to column 4, line 10). Given that Matsushita et al. suggest the use of an antibody that is broadly reactive with a number of HIV isolates (see page 200), it would have been obvious for one of ordinary skill in the art to use the 3B3 antibody in the immunotoxin disclosed by Matsushita et al. Moreover, it would have been equally obvious for one of ordinary skill to incorporate the PE modifications disclosed by Pastan et al. in order to take advantage of the resulting increase in cytotoxicity. It should be noted that while the incorporation of immunotoxins in kits is not explicitly disclosed by Matsushita et al., said incorporation would have been obvious to one of ordinary skill in the art in order to reduce cost and ease preparation time. It should be noted that while the sequence of the 3B3 antibody is not explicitly disclosed, it is deemed in absence of evidence to the contrary to be the same as that of the 3B3 of the instant application (SEQ ID NO:1).

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9, 11, 52, 55, 57, 68-75 and 77 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claims 1, 52, 68 and 74 are rendered vague and indefinite by the use of the phrase "which 3B3 Fv consists of a VH chain and a VL chain encoded by SEQ ID NO:2". It is unclear whether Applicant is stating that both the VH and VL chains are encompassed by SEQ ID NO:2 or both the VH and VL are individually encoded by SEQ ID NO:2.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in black ink, appearing to read "Robert A. Zeman". The signature is fluid and cursive, with the first name "Robert" and last name "Zeman" clearly distinguishable.

April 30, 2007